REMARKS

Claims 19-32 and 35-54 are now pending in the present application, claims 1-18 and 33-34 having been canceled, and new claims 36-54 having been added by the present amendment. New claims 41-43 are supported by the specification at, e.g., page 4, lines 26-28, page 6, and page 18, lines 5-8. New claims 36-40 further limit the kit claimed in original claim 26. For example, new claims 36 and 37 state that the kit further comprises instructions for use. Support for new claims 36 and 37 can be found in the specification at, e.g., page 5, lines 12-15. New claims 38-40 limit the antibody supplied in the kit to a monoclonal antibody, which is disclosed at, e.g., page 5, line 3, and page 8, lines 1-2 and 25-29. New claims 44-49 are dependent claims that further limit claims reciting methods for obtaining an antibody to a monoclonal antibody. Support for new claims 44, 46 and 49 can be found at, e.g., page 5, lines 1-5. Support for new claims 45, 47 and 48 can be found at, e.g., page 29, lines 3-26. New claims 50-54 further limit the method claimed in original claim 32, and are supported at, e.g., page 5, lines 1-5, and by the originally filed claims. Applicants expressly reserve their rights to prosecute the canceled claims by way of a divisional application.

Claims 22, 24, 26, 28 and 29 have been amended to correct grammatical or typographical errors. Claim 32 has been amended for clarity. No new matter has been added.

Rejections under 35 U.S.C. §102

The Examiner has rejected claims 19-21 and 32 for lack of novelty in view of Elthon *et al.* (U.S. Patent No. 6,268,548; herein, "Elthon"). For the sake of completeness and easy reference, we reproduce the Examiner's statements regarding Elthon, in their entirety, here (Office action at page 3):

> Elthon et al. teach that Hsp70B protein is associated with environmental stress (see Col. 1, Background Information) (*sic.*). Elthon et al. also isolate a (*sic.*) monoclonal antibody against Hsp70B, and this antibody can be used to detect cells exposed to a (*sic.*) stressful environment (see Figures 6-7) (*sic.*). With respect to claim 21, having a relative titre index greater than one is inherently anticipated by Elthon et al. in processing isolation of antibody of Hsp70B.

This ground for rejection is respectfully traversed. The rejected claims cover antibodies that specifically bind Hsp70B′ (claims 19-21) and methods of using such antibodies to determine whether a cell has been exposed to a stressful environment or a stressful substance (claim 32). To anticipate these claims, Elthon must disclose an antibody or a method that falls within the scope of the present claims; the test for anticipation is a test of identity. *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). For the reasons that follow, Elthon does not disclose what Applicants now claim.

The antibody Applicants claim is one that specifically binds Hsp70**B′** (emphasis on "B-prime"), whereas Elthon's antibody specifically binds Hsp70 (not B-prime). Although Elthon's description of Fig. 6 (to which the Examiner referred; at column 4) *does* include the term "HSP70B," that term is deceptive – it does not, in fact, designate an antibody that specifically binds Hsp70B (or Hsp70B′). Elthon used three different monoclonal antibodies to identify Hsp70, and those antibodies were referred to as Hsp70A, Hsp70B, and Hsp70C. More specifically, the figure legend reads, in part (emphasis added):

> "[i]mmunoblots...were prepared and probed with the *Mabs to HSP70*....The top panels illustrate blots probed with Mabs HSP70A, HSP70B, and HSP70C *which identify the 70kD species*.

Thus, Elthon's "Hsp70B" monoclonal antibody is not a monoclonal antibody against the Hsp70B protein, but rather the second of three monoclonal antibodies against Hsp70; the first was designated "A", the second was designated "B", and the third was designated "C". Elthon's descriptions of Figures 8 and 12 (columns 4 and 5, respectively) also make it clear that "Hsp70B" refers to a monoclonal antibody against Hsp70.

Hsp70, Hsp70B, and Hsp70B′ are distinct proteins, and Elthon's antibodies, which specifically bind Hsp70, would not specifically bind Hsp70B′ (as is required by Applicants claim 19). Moreover, even if Elthon's anti-Hsp70 antibody also bound to Hsp70B′, it would not fall within Applicants' claim. The claim term "specifically binds" limits the claimed antibody to one

that binds Hsp70B′ to the exclusion of other Hsp proteins, including Hsp70. In their specification, Applicants teach (page 3, lines 17-22):

> [t]he present invention is based, in part, on the identification of immunogenic peptide sequences from the human Hsp70B′ protein. Antibodies that specifically bind this protein can be used to distinguish between the expression of HSC70/HSP70 proteins, which occurs while a cell is functioning normally and when it is responding to stress, and the Hsp70B′ protein, which is only produced in response to stress.

Clearly, antibodies that specifically bind Hsp70B′ (as claimed) do not also specifically bind Hsp70 (as did Elthon's antibodies). As Elthon's antibody and the antibodies now claimed are different, Elthon cannot anticipate claims 19-21.

Claim 32, which covers a method of determining whether a cell has been exposed to a stressful environment or a stressful substance, requires an antibody that specifically binds Hsp70B′. As established above, Elthon does not disclose antibodies against Hsp70B′ or Hsp70B. Elthon cannot, therefore, anticipate claim 32.

The Examiner rejected claims 22-31 and 35 under 35 U.S.C. § 102(a) as anticipated by Rosen *et al.* (U.S. Publication No. 20030064072; Office action at page 3; herein, "Rosen"). 35 U.S.C. § 102 reads, in relevant part (emphasis added):

> A person shall be entitled to a patent unless (a) the invention was known or used by others in this country, or patented *or described in a printed publication* in this or a foreign country, *before the invention thereof by the applicant* for patent ...(emphasis added).

Rosen was published on April 3, 2003, and the present application was filed on December 7, 2000. Thus, regardless of the subject matter Rosen discloses, there is no anticipation under 35 U.S.C. § 102(a); the invention could not have been described by Rosen before the invention thereof by Applicants.

Nor does Applicants' representative see any other basis for applying Rosen under § 102 of the statute. If the Examiner intended to make the present rejection under 35 U.S.C. § 102(e), Applicants respectfully request evidence that the allegedly relevant material is entitled to a filing date earlier than the August 10, 2001, filing date of U.S.S.N. 09/925,302 (the application that published as 20030065072

(Rosen)). That filing date (August 10, 2001) is later than Applicants' filing date (December 7, 2000). Moreover, as Rosen is a continuation-in-part of an earlier filed application (PCT/US00/05918, filed March 8, 2000), it is not a given that the allegedly relevant material was disclosed in the earlier filed PCT application. Should the Examiner maintain that Rosen anticipates any of the presently pending claims, the favor of a telephone call to the undersigned is kindly requested.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 19-21 under 35 U.S.C. § 103(a) as unpatentable over Leung *et al.* (*Biochem. J.* 267:125-132, 1990; herein, "Leung"). The Examiner's statements in support of the rejection follow in their entirety (Office action at page 4):

> Leung et al. characterize the human heat-shock genes, encoded the Hsp70B proteins. (See abstract and Figure 1). This Office takes the position that such information would have been obvious to enable one skilled in the art to make corresponding antibodies because the Board of Patent Appeals and Interferences (*sic*) has taken the position that once an antigen has been isolated, the manufacture of monoclonal (*sic.*) antibodies against it is *prima facie* obvious. See *Ex parte Erlich*, 3 USPQ 2d 1011 (Bd. Pat. App. & Inter. 1987) and *Ex parte Sugimoto*, 14 USPQ 2d 1312 (Bd. Pat. App. & Inter. 1990).

This ground for rejection is respectfully traversed. Leung cannot render the subject matter of claims 19-21 obvious, nor can the cited cases, *Erlich and Sugimoto*, support the broad proposition that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious.

Leung discloses the nucleotide sequence of a human HSP70B′ gene and the predicted amino acid sequence (*see* Fig. 2). Leung does not, however, disclose or suggest making antibodies that specifically bind the Hsp70B′ protein. Absent such a disclosure, there can be no *prima facie* case of obviousness. There is a well-established legal standard for obviousness: there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; there must be a reasonable expectation of success; *and* the prior art reference must teach or suggest all the claim limitations. Moreover, the suggestion to make the claimed combination and the expectation of

success must both be found in the prior art, not in Applicants' disclosure. MPEP at 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Leung meets none of these criteria, and that failure cannot be remedied by the cited decisions.

The facts upon which the Board of Patent Appeal and Interferences ("the Board") found obviousness in *Erlich* and *Sugimoto* are very different from the facts in the present case.

In *Erlich*, the Board affirmed the Examiner's rejection of claims to monoclonal antibodies against human fibroblast interferon, based on numerous prior art references (3 USPQ 2d at 1012). Two of those references ("Stewart" and "Ganfield") disclosed that human fibroblast interferon and human leukocyte interferon were antigenic (*Id.* at 1014). A third reference, "Kohler and Milstein" (*Id.*) disclosed a basic method of making monoclonal antibodies (this reference was cited in the specification of the application at issue), and a fourth reference, "Secher" taught how to use that method to make monoclonal antibodies against human leukocyte interferon (*Id.*). Based on these substantial teachings, the Board found that the claimed subject matter was obvious because one "would have been motivated to produce monoclonal antibodies specific for human fibroblast interferon using the method of Kohler and Milstein with a reasonable expectation of success" (*Id.* at 1016, emphasis added). In *Erlich*, the prior art references satisfied the legal standard standard for obviousness. In the present case, the single reference cited by the Examiner (Leung) does not.

The Board did note, "once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies" (*Id.* at 1015). However, this statement must be read in light of all the facts in *Erlich*, where the Board relied heavily on Secher as a showing "that the basic method of Kohler and Milstein may be readily used and adapted for various antigens such as an interferon" (*Id.*). Thus, although the Board stated that "it would have been obvious...to use the basic method of Kohler and Milstein to form monoclonal antibodies specific for human fibroblast interferon since human fibroblast interferon was a known antigen," the Board emphasized that "[o]ne would have approached this project with a reasonable expectation of success in view of the Secher publication in that the Secher publication evidenced that one may

successfully adapt the Kohler and Milstein method to produce monoclonal antibodies specific for a human interferon" (*Id.*, emphasis added). It was not a simple disclosure of an antigen that rendered monoclonal antibodies against it obvious.

In *Sugimoto*, the Board affirmed the obviousness rejection of claims to methods for producing human Soluble Immune Response Suppressor (hIRS) (14 USPQ 2d 1312). In the claimed process, as summarized by the Board:

> human cells capable of producing hIRS are fused with a human lymphoblastoid line to produce hybridoma cells capable of producing said suppressor. The hybridoma is implanted in a non-human warm-blooded animal wherein the cells are permitted to multiply. Subsequently, the tumor from the non-human animal is extracted and disaggregated to obtain the multiplied hybridoma cells. Thereafter said cells are cultured *in vitro* to accumulate hIRS, which is then recovered (*Id.*).

The Board agreed with the Examiner that

> it would have been obvious to select cells such as human T-lymphotocytes as taught by Rocklin et al, which produce a human immune response suppressor factor, and to substitute these cells for the erythropoietin producing cells in the process as taught by Sugimoto et al to obtain enhanced production of human Soluble Immune Response Suppressor (*Id.*).

The Board did not state anywhere that the isolation of hIRS rendered the manufacture of monoclonal antibodies against hIRS *prima facie* obvious. Indeed, *Sugimoto* did not involve monoclonal antibody production at all. *Sugimoto* in no way takes the position that, once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. Given that Leung and *Erlich* do no more to establish obviousness, this ground for rejection should be withdrawn.

Priority under 35 U.S.C. §§ 119 and 120

The Examiner has acknowledged a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f), and has noted that none of the certified copies of the priority documents has been received (see the Office Action Summary ¶ 13). However, Applicants have not claimed foreign priority. In the Combined Declaration and Power of Attorney filed May 9, 2001, Applicants

listed PCT Application No. US00/33341, but Applicants did not claim priority to this foreign application. Thus, no certified priority documents are required.

The Filing Receipt mailed September 10, 2001 and the Updated Filing Receipt mailed November 4, 2002 incorrectly noted foreign priority to the PCT Application (and correctly noted domestic priority to U.S. Application No. 60/169,575). Applicants will file separately a request to correct the filing receipt to claim priority only to U.S. Application No. 60/169,575.

Concluding Remarks

In view of the foregoing, the present claims are believed to be in condition for allowance, which action is respectfully requested.

Enclosed is a Petition for Extension of Time with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: January 27, 2004

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